

Remarks

The Examiner has rejected claims 1-6 as anticipated by Belanger et al., U.S. Patent No. 5,443,981 and has rejected claims 1-4, 7-12, and 18 as anticipated by Breton et al., U.S. Publ. No. 2006/0069505 as evidenced by the Molano et al. reference (J. Cell Biol. 85:199-212, 1980). The Examiner has further rejected claims 1-4 and 7-18 as obvious in light of the combination of Breton and Modi, U.S. Patent No. 6,221,378, again as evidenced by the Molano reference.

Applicant has amended claim 1, rewritten claim 15 as an independent claim, and amended the dependency of each of claims 16-18. Entry of these amendments is respectfully requested.

In addition, Applicant presents herewith a declaration from an expert in the field of drug delivery systems, Randall J. Mersny, discussing the relevance of the cited references to the claims of the present invention.

I. Claims 1-6 are not anticipated by Belanger.

First, Applicant's amendment to claim 1 to require that the adjuvant is present in an amount sufficient to increase the permeability of paracellular pathways in vivo should suffice to eliminate the anticipation rejection. The Belanger reference does not discuss increasing the permeability of paracellular pathways whatsoever, nor is paracellular pathway permeability *necessarily* increased in vivo by administering any amount of BCA or PMSF or any other compound discussed in Belanger. (See, e.g. Mersny declaration ¶¶ 11 and 12.) Belanger thus cannot be considered anticipatory, either explicitly or under the principals of inherency.

Second, the Examiner has stated that a membrane fraction of a fungal cell "is reactive with BCA (pharmaceutically active compound, peptide, having a hydrophilic moiety)." (2/1/8 OA, p. 3.) The Examiner has also stated that "endoproteolytic activity is inhibited by the protease

inhibitor PMSF (pharmaceutically active compound).” (2/1/8 OA, p. 3.) It therefore is understood that the Examiner has found BCA and PMSF to be the compounds that anticipate the “pharmaceutically active compound” element of claims 1-6.

However, neither BCA nor PMSF is a pharmaceutically active compound. As discussed by Dr. Mrsny in the Rule 132 declaration submitted herewith, mere reactivity of a fungal cell or fragment thereof with various chemicals does not constitute a pharmaceutical application.

Pharmaceutical applications require materials having therapeutic qualities. (Mrsny declaration, ¶ 12.)

BCA (bicinchoninic acid) is commonly used in protein research to determine the total protein level in a solution precisely because it reacts with protein. More specifically, in a BCA assay, a reaction between the BCA solution and the peptide bonds in protein takes place in a proportional fashion so that the reduction of a particular element present in the BCA solution indicates that the quantity of protein is present in the test solution. Similarly, PMSF (phenylmethylsulphonyl fluoride) is a chemical commonly used in protein laboratories in the extraction and purification of proteins. PMSF inhibits particular proteases, and therefore is used to prevent those proteases from digesting the target proteins at cell lysis.

In light of the fact that (1) Belanger does not discuss paracellular pathways, and (2) neither BCA nor PMSF have therapeutic qualities and, therefore, neither constitutes a pharmaceutically active compound as required by the claims, it is believed that the Belanger reference fails to anticipate claim 1. Withdrawal of the rejection of claim 1 and dependent claims 2-6 is requested.

II. Claims 1-4, 7-12, and 18 are not anticipated by Breton.

The Breton reference likewise does not disclose increasing the permeability of paracellular pathways or absorption of pharmaceutical compounds via paracellular pathways as required in amended claims 1 and 15. As noted by Dr. Mrsny, Breton discusses the effects of co-administration of lactic acid bacteria with a carotenoid compound for skin protection, but does nothing to suggest that the presence of the lactic acid improves uptake of the carotenoid or vice-versa. To the contrary, the carotenoids listed in Breton are frequently found in the diet and are readily absorbed without co-administration of lactic acid bacterium or yeast. (Mrsny declaration, ¶ 13.) The disclosed bacteria therefore do not increase permeability of the paracellular pathways in vivo and is not an adjuvant, which is defined as a substance added to assist the action of the principal ingredient. It is believed that claims 1-4, 7-12, and 18, as amended, define over the Breton reference. Withdrawal of the rejection is therefore requested.

III. Claims 1-4 and 7-18 are not obvious in light of the combination of Breton and Modi.

The Examiner correctly states that the Breton reference does not teach the existence of a paracellular pathway for drug delivery. (2/1/8 OA, p. 6.) However, for a number of reasons, the Modi reference does not cure that failure.

First, the Examiner states that “since the invention of Modi yielded beneficial results in drug delivery system, one of ordinary skill in the art would have been motivated to make the modifications [of Modi to Breton].” (2/1/8 OA, p. 7.) However, the Examiner also notes that the benefit of Modi is a delivery system that preserves protease activity and protects molecules from premature degradation in vivo. This benefit is not needed for delivery of the Breton composition, since Breton teaches that the probiotic lactic acid/carotenoid combination can be delivered through any food or pharmaceutical product, including simply adding to milk, yoghurt, infant

formula, or cereal, or by putting the supplement in a capsule or tablet form. Breton further states that “methods for preparing the carrier are common knowledge.” (Breton at ¶ 26.) Breton does not require preservation of protease activity and protection of premature degradation in vivo: the complex micellar drug delivery system disclosed in Modi is totally unnecessary for delivering the Breton composition. A person of skill in the art would therefore never look to the Modi system as a means for delivering the Breton composition. There is no motivation to combine the references and the obviousness rejection should be withdrawn on that basis alone.

Second, the Examiner’s rejection quotes the Modi reference, stating that “Modi teaches protein drug was encapsulated in mixed micelles which allows opening of paracellular junctions...” (2/1/8 OA, p. 6; Modi, col. 2, lines 62-65.) Modi further notes that it is the small size provided by encapsulation in micelle form that allows for efficient penetration. (Modi, col. 3, lines 7-10.) In other words, it is the micellar format, not the presence of an adjuvant, that allegedly allows penetration of the tight paracellular junctions.

As noted by Dr. Mrsny, the Modi reference is primarily directed to mixed micelle complexes that can be sprayed into the nose or into the oral cavity. (Mrsny declaration, ¶ 14.) This is because the complexes described in the Modi publication are not sufficiently stable to reach the intestinal mucosa in an intact and bioactive form, and can function only at those sites. (Mrsny declaration, ¶ 14.) More importantly, Dr. Mrsny notes that the protection of labile materials and identification of methods of opening paracellular junctions are two separate issues. (Mrsny declaration, ¶ 15.) The Modi reference thus is directed primarily to solving the first issue and tangentially notes that it believes to have made an impact on the second issue. (As noted above, however, it is the micelle presentation that is believed to have impacted paracellular

uptake, not the presence of an adjuvant.) As a result, the Modi reference is inapplicable to the problem of delivering an orally administered pharmaceutical of the type disclosed in Breton.

With respect to the Molano reference, which the Examiner does not rely on as the basis for rejection per se, Molano certainly indicates that chitin is a component of a yeast cell wall. However, Molano does not define or describe the actions of yeast or chitin on paracellular pathways. Mere presence of chitin does not automatically result in a modulation of tight junction functions. (Mrsny declaration, ¶ 16.)

The Examiner states that “it is apparent that one of the ordinary skills [*sic*] in the art would have had a reasonable expectation of success in producing the claimed invention” based on the teachings of Breton and Modi. (2/1/8 OA, p. 7.) However, Dr. Mrsny, who undeniably is a person of skill in the art, disagrees, noting that in fact, the use of fungal cells and derivatives thereof to increase mucosal permeability would not be expected, even in light of the cited references. (Mrsny declaration, ¶ 6.) Withdrawal of the rejection under 35 U.S.C. § 103 is therefore requested.

Conclusion

It is submitted that each of claims 1-18 is pending and each is in compliance with 35 U.S.C. §§ 102 and 103. Applicant hereby requests a three-month extension of time for reply, the fee for which is submitted herewith. No additional fees are believed to be due with the submission of this communication. Nevertheless, the Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1170. The Examiner is encouraged to contact the undersigned by phone if questions remain after consideration of this response, or if such would otherwise facilitate prosecution.

Respectfully submitted,

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